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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/758,773	01/16/2004	Seng H. Cheng	07680.0018	6298

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EXAMINER	
CHEN, SHIN LIN	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/758,773	CHENG ET AL.	
	Examiner	Art Unit	
	Shin-Lin Chen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *8-3-06 & 3-27-07*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,4,6-20,22 and 36-40* is/are pending in the application.

4a) Of the above claim(s) *10-12,19 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4,6-9,13-18,20 and 36-40* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6-21-04 & 3-27-07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's election of group I, claims 1-9, 13-18, 20 and 21, in the reply filed on 8-3-06 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

2. Claims 10-12, 19 and 22-35 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 8-3-06.

Applicants' request for resumption of examination filed 3-27-07 has been entered. Action of merit follows. Applicants' amendment filed 3-27-07 has been entered. Claims 1, 6, 14, 19, 20 and 22 have been amended. Claims 2, 5, 21 and 23-35 have been canceled. Claims 36-40 have been added. Claims 1, 3, 4, 6-20, 22 and 36-40 are pending. Claims 1, 3, 4, 6-9, 13-18, 20 and 36-40 are under consideration.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claims 8, 14, 38 and 40 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "GL-3" in claims 8 and 38 is vague and renders the claims indefinite. The term "GL-3" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claims. Spelling out the term " GL-3" would be remedial.

The term "AAV" in claims 14 and 40 is vague and renders the claims indefinite. The term "AAV" is an abbreviation that can stand for various meanings. It is unclear what meaning is intended in the claims. Spelling out the term " AAV" would be remedial.

Claim Rejections - 35 USC § 112

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1, 3, 4, 6-9, 13-18, 20 and 36-40 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to a method of treating a subject having a lysosomal storage disease, such as Fabry disease, by first administering a gene therapy vector, such as a viral vector or an AAV vector, encoding a lysosomal hydrolase under the control of at least one tissue specific regulatory element, such as a liver specific promoter or a tissue specific enhancer, and then administering an exogenously produced natural or recombinant lysosomal hydrolase or a method of treating a subject having Fabry disease comprising first administering a gene therapy vector encoding alpha-galactosidase A under the control of a human albumin promoter and 2

copies of a human prothrombin enhancer and then administering an exogenously produced natural or recombinant alpha-galactosidase A. Claims 6 and 37 specify a lesser amount of natural or recombinant lysosomal hydrolase is administered than would be administered if the subject had not been administered a gene therapy vector encoding a lysosomal hydrolase or had been administered a gene therapy vector without a tissue specific promoter. Claims 8 and 38 specify the treatment results in a decrease in GL-3 in the subject compared to the GL-3 level in the subject before treatment.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). See also In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. In re Angstadt, 537 F.2d 498, 504, 190 USPQ 214, 219 (CCPA 1976). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to: (A) The breadth of the claims; (B) The nature of the invention; (C) The state of the prior art; (D) The level of one of ordinary skill; (E) The level of predictability in the art; (F) The amount of direction provided by the inventor; (G) The existence of working examples; and (H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The specification discloses generation of adeno-associated viral vector AAV2/CMVHI-alphagal expressing human alpha-galactosidase under the control of CMV promoter/enhancer and vector AAV2/DC190-alphagal expressing human alpha-galactosidase under the control of human serum albumin promoter and 2 copies of the human prothrombin enhancer (e.g. Example

2). Administration of AAV2/CMVHI-alphagal into immunosupressed mice via the tail vein results in expression of alpha-galactosidase in liver, hearts and spleens and reduction of accumulated GL-3 level in those organs but none in the kidney. Administration of AAV2/DC-190-alphagal into immuno-competent mice (BALB/c) via tail vein results in 2 to 3 logs higher expression of alpha-galactosidase in those organs, including kidney (Examples 4-6). The use of liver-specific promoter/enhancer DC190 results in a reduced host immune response to the encoded human alpha-galactosidase in the AAV2/DC-190-alphagal-treated mice and sustained expression levels of the enzyme (Examples 7-8). Basal levels of GL-3 in the liver, heart and spleen were attained in Fabry mice treated with systemic administration of AAV2/DC-190-alphagal vector and about 40% reduction in substrate levels in the kidney was also achieved (Example 9). The claims encompass treatment of any lysosomal storage disease in a subject by first administering any gene therapy vector encoding a lysosomal hydrolase under the control of at least one tissue specific regulatory element and then administering an exogenously produced natural or recombinant lysosomal hydrolase to a subject via various administration routes or treatment of a subject having Fabry disease comprising first administering any gene therapy vector encoding alpha-galactosidase A under the control of a human albumin promoter and 2 copies of a human prothrombin enhancer and then administering an exogenously produced natural or recombinant alpha-galactosidase A via various administration routes.

The specification fails to provide adequate guidance and evidence for how to treat a subject having various lysosomal storage diseases by first administering any gene therapy vector encoding a lysosomal hydrolase under the control of at least one tissue specific regulatory element and then administering an exogenously produced natural or recombinant lysosomal

hydrolase to a subject via various administration routes so as to provide therapeutic effect and to ameliorate the symptoms of the diseases. The specification also fails to provide adequate guidance and evidence for how to treat a subject having Fabry disease comprising first administering any gene therapy vector encoding alpha-galactosidase A under the control of a human albumin promoter and 2 copies of a human prothrombin enhancer and then administering an exogenously produced natural or recombinant alpha-galactosidase A via various administration routes so as to provide therapeutic effect and to ameliorate the symptoms of the diseases.

The claims read on using polynucleotides encoding various lysosomal hydrolases to treat various lysosomal storage diseases in a subject therefore, the claims read on gene therapy in vivo. The nature of the invention being gene therapy, the state of the prior art was not well developed and was highly unpredictable at the time of filing. While progress has been made in recent years for gene transfer *in vivo*, vector targeting to desired tissues *in vivo* continues to be unpredictable and inefficient as supported by numerous teachings available in the art. For example, Deonarain, M., 1998 (Expert Opin. Ther. Pat., Vol. 8, pages 53-69, IDS) indicates that one of the biggest problems hampering successful gene therapy is the "ability to target a gene to a significant population of cells and express it at adequate levels for a long enough period of time" (page 53, first paragraph). Verma et al., Sept. 1997 (Nature, Vol. 389, pages 239-242, IDS) reviews vectors known in the art for use in gene therapy and discusses problems associated with each type of vector. The teachings of Verma indicate a resolution to vector targeting has not been achieved in the art (see entire article). Verma also teaches appropriate regulatory elements may improve expression, but it is unpredictable what tissues such regulatory elements

target (page 240, sentence bridging columns 2 and 3). Verma states that "The Achilles heel of gene therapy is gene delivery, and this is the aspect that we will concentrate on here. Thus far, the problem has been an inability to deliver genes efficiently and to obtain sustained expression." (e.g. p. 239, column 3).

Eck et al., 1996 (Goodman & Gilman's The Pharmacological Basis of Therapeutics, McGraw-Hill, New York, p. 77-101, IDS) reports that numerous factors complicate in vivo gene therapy with respect to predictably achieving levels and duration of gene expression which have not been shown to be overcome by routine experimentation. These include, the fate of the DNA vector itself (volume of distribution, rate of clearance into the tissues, etc.), the *in vivo* consequences of altered gene expression and protein function, the fraction of vector taken up by the target cell population, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA produced, the amount and stability of the protein produced, and the protein's compartmentalization within the cell, or its secretory fate, once produced. These factors differ dramatically based on the vector used, the protein being produced, and the disease being treated (e,g, bridging pages 81-82). The specification fails to provide adequate guidance for how to overcome any of the above unpredictable parameters in the gene transfer art such that one would be able to treat various lysosomal storage diseases with the claimed method in vivo.

In addition, Gorecki, D., 2001 (Expert Opin. Emerging Drugs, 6(2): 187-198, IDS) reports that "the choice of vectors and delivery routes depends on the nature of the target cells and the required levels and stability of expression" for gene therapy, and obstacles to gene therapy *in vivo* include "the development of effective clinical products" and "the low levels and

stability of expression and immune responses to vectors and/or gene products" (e.g. abstract). It was known in the art that administration route of an expression construct expressing a gene product of interest plays an important role in gene transfer *in vivo*. The fate of DNA construct, the amount of DNA reaches its targeted site, the stability of mRNA and protein expressed, and the biological function of the protein all depend on the administration route in gene transfer *in vivo*.

Further, the state of the art of treating lysosomal storage diseases in vivo was unpredictable at the time of the invention. Pastores et al., 2005 (Expert Opin. Emerging Drugs, Vol. 10, No. 4, p. 891-902) discloses that "[t]he lysosomal disorders (LSDs) are inborn errors of metabolism associated with a disruption in the hydrolysis and transport of diverse macromolecules within the endo-lysosomal compartment ... Various other protein defects have been established as causative in certain subtypes" (p. 891, section "Background"). "About 50 distinct clinical entities are classified within this disease group" and "Characteristics features of an LSD may include dysmorphic facial features, organomegaly, skeletal problems and CNS dysfunction. There is broad heterogeneity in clinical expression within disease types, which, in the single hydrolase-deficiency disorders, partly reflects the presence or absence of residual enzyme activity ... The wide variability in clinical expression for most subtypes, even among affected members of the same family, suggests that ultimate disease course is likely to be influenced by several modifiers" (e.g. p. 892, left column). Pastores points out that several disorders associated with defects in membrane proteins and these diseases will most likely not responsive to enzyme therapy or substrate reduction. "Diseases associated with primary CNS involvement present major challenges that are beyond the access limitations imposed by the

blood- and CSF-barrier" (e.g. p. 898, left column, second paragraph). "Beyond the issues relating to treatment of the CNS pathology, the multisystemic nature of LSDs and the possibility of "sanctuaries" (i.e., tissue sites of storage that may not be fully accessible to small molecules, enzyme- or cell-based therapy; or may be unresponsive to therapy because of alternative downstream disease mechanisms that may be irreversible) raise the prospect that only partial responses may occur, despite prolonged treatment" (e.g. p. 898, last paragraph, bridging left and right columns). Wraith, J.E., 2006 (J. of inherit. Metab. Dis., Vol. 29, p. 442-447) reports that there is an inability to target the infused enzymes to specific sites of pathology, especially the central nervous system and a lack of suitable animal models of the human disease in which to evaluate the new therapy (intravenous infusion of lysosomal enzymes) (e.g. p. 442, right column). There are only a limited number of enzyme replacement therapies currently available for lysosomal storage disorders (LSDs) (e.g. Table 1). Eto et al., 2004 (J. Inherit. Metab. Dis., Vol. 27, p. 411-415) also points out that "[m]ost lysosomal storage diseases have central nervous system (CNS) involvement. No effective treatment is available at present" (e.g. p. 411, Summary). In view of the diverse lysosomal storage diseases or disorders, the broad scope of heterogeneity of clinical expression within a type of LSD, limited number of enzyme replacement therapy available, and the difficulties in treating LSDs involving CNS, one skilled in the art at the time of the invention would not know how to treat various LSDs by using any vector expressing various lysosomal hydrolases under the control of a tissue specific promoter in combination with an enzyme replacement therapy via various administration routes such that therapeutic effect can be obtained and pathological symptoms can be ameliorated in vivo.

Claims 20 and 36-40 read on treating Fabry disease with a gene therapy vector encoding alpha-galactosidase A in combination with a alpha-galactosidase A enzyme therapy. The specification only discloses the reduction of GL-3 in liver, heart, spleen and kidney by using the particular AAV2/CD-190-alphagal vector. The specification fails to provide specific guidance and evidence for how to treat Fabry disease with a gene therapy vector encoding alpha-galactosidase A in combination with a alpha-galactosidase A enzyme therapy such that therapeutic effect can be obtained and pathological symptoms can be ameliorated in vivo. There is no correlation between reduction of GL-3 level in the organs and treatment of Fabry disease in a subject, i.e. amelioration of pathological symptoms of Fabry disease in vivo. Reduction of GL-3 in organs in a subject does not necessarily mean that the Fabry disease is treated. Absent specific guidance and evidence, one skilled in the art at the time of the invention would not know how to treat Fabry disease with a gene therapy vector encoding alpha-galactosidase A in combination with a alpha-galactosidase A enzyme therapy such that therapeutic effect can be obtained and pathological symptoms can be ameliorated in vivo.

In addition to the unpredictability in gene therapy and enzyme replacement therapy in vivo, the biological functions of various lysosomal hydrolase proteins differ from each other. The claims read on treating any lysosomal storage disease with a gene therapy vector encoding any lysosomal hydrolase in combination with any lysosomal hydrolase protein. The biological function of a protein from mere amino acid sequence was unpredictable at the time of the invention. It was known in the art that the amino acid sequence of a polypeptide determines its structural and functional properties (including half-life), and predictability of which amino acid(s) can be removed from or added to a polypeptide's sequence and still result in similar

activity or result in stabilization of the protein is extremely complex, and well outside the realm of routine experimentation. Rudinger, 1976 (Peptide Hormones, Parsons, University Park Press, Baltimore, p. 1-7) points out that "The significance of particular amino acids and sequences for different aspects of biological activity cannot be predicted *a priori* but must be determined from case to case by painstaking experimental study" (e.g. p. 6). Kaye et al., 1990 (Proc. Natl. Acad. Sci. USA, Vol. 87, pp. 6922-6926) discloses that a single amino acid substitution results in a retinoblastoma protein defective in phosphorylation and oncoprotein binding (e.g. title). In addition, Skolnick et al., 2000 (Trends in Biotech, Vol. 18, p. 34-39) states "Sequence-based methods for function prediction are inadequate because of the multifunctional nature of proteins. However, just knowing the structure of the protein is also insufficient for prediction of multiple functional sites. Structural descriptors for protein functional sites are crucial for unlocking the secrets in both the sequence and structural-genomics projects" (e.g. abstract). Skolnick further states that "Knowing a protein's structure does not necessarily tell you its function" and "Because proteins can have similar folds but different functions, determining the structure of a protein may or may not tell you something about its function" (e.g. p. 36, box 2). Therefore, biological function of a protein was unpredictable from mere amino acid sequence at the time of the invention. The biological functions of the lysosomal hydrolase proteins encoded by different hydrolase genes were unpredictable at the time of the invention and the specification fails to provide adequate guidance and evidence for whether those hydrolase proteins would be able to provide therapeutic effect in treating various LSDs in vivo. Absent such guidance, one skilled in the art at the time of the invention would not know how to use those various polynucleotides

encoding hydrolase proteins in combination with hydrolase proteins for the claimed treatment of LSDs in a subject.

For the reasons discussed above, it would have required undue experimentation for one skilled in the art at the time of the invention to practice over the full scope of the invention claimed. This is particularly true given the nature of the invention, the state of the prior art, the breadth of the claims, the amount of experimentation necessary, the level of ordinary skill which is high, the working examples provided and scarcity of guidance in the specification, and the unpredictable nature of the art.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shin-Lin Chen whose telephone number is (571) 272-0726. The examiner can normally be reached on Monday to Friday from 9:30 am to 6 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for this group is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Shin-Lin Chen, Ph.D.

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